

## Risk factors associated with moderate-to-severe renal dysfunction among heart transplant patients: results from the CAPRI study

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### Abstract

The longer survival of patients with heart transplantation (HT) favors calcineurin inhibitor-related chronic kidney disease (CKD). It behoves to identify risk factors. At 14 Spanish centers, data on 1062 adult patients with HT (age  $59.2 \pm 12.3$  yr, 82.5% men) were collected at routine follow-up examinations. Glomerular filtration rate, GFR, was estimated using the four-variable MDRD equation, and moderate-or-severe renal dysfunction (MSRD) was defined as K/DOQI stage 3 CKD or worse. Time since transplant ranged from one month to 22 yr (mean 6.7 yr). At assessment, 26.6% of patients were diabetic and 63.9% hypertensive; 53.9% were taking cyclosporine and 33.1% tacrolimus; and 61.4% had MSRD. Among patients on cyclosporine or tacrolimus at assessment, multivariate logistic regression identified male sex (OR 0.44), pre- and post-HT creatinine (2.73 and 3.13 per mg/dL), age at transplant (1.06 per yr), time since transplant (1.05 per yr), and tacrolimus (0.65) as independent positive or negative predictors of MSRD. It is concluded that female sex, pre- and one-month post-HT serum creatinine, age at transplant, time since transplant, and immunosuppression with cyclosporine rather than tacrolimus may all be risk factors for development of CKD  $\geq$  stage 3 by patients with HT.

The life expectancy of patients with heart transplantation (HT) is steadily increasing. According to the ISHLT Registry report for 2008, the estimated median survival time among patients surviving the first yr after transplantation, calculated from data for 1982–2006, is 13 yr (1). Longer survival brings with it a greater risk of non-cardiac morbidities because of normal aging (such as diabetes), immunosuppression (such as neoplasia and infections), and adverse side effects of immunosuppressive therapy that do not derive directly from immunosuppression *per se*. In particular, the nephrotoxic effects of calcineurin inhibitors (CNI) have been of concern virtually since the introduction of cyclosporine (2), both on their own account and because of the cardiovascular and other non-renal pathological implications of renal dysfunction (3). Post-transplant chronic kidney disease (CKD) of K/DOQI (4) stage 4 or worse multiplies four-fold the death rate among all non-renal solid organ transplant patients (5), and the five-yr survival of patients with HT on dialysis for CKD is only half that of dialyzed patients with CKD with no organ graft (19% as against 40%) (6). The ISHLT-Registry-based Kaplan–Meier estimate of the intrinsic probability of an patient with HT who survives 13 yr developing severe renal dysfunction (serum creatinine  $> 2.5$  mg/dL, dialysis or kidney transplant) exceeds 40% (1); the current actual prevalence of CKD of K/DOQI stage 3 or worse among Spanish patients with HT who survive more than 9.5 yr is 67% (7).

The magnitude of the problem of post-transplant CKD makes it necessary to characterize patients at greatest risk, if only because this will facilitate preliminary evaluation of preventive strategies (8). Most studies that have investigated this issue have identified risk factors analogous to those of CKD of non-transplant patients, including age, female sex, pre-transplant arterial hypertension and diabetes mellitus, together with pre-transplant renal dysfunction and post-operative acute kidney failure (3, 5). There has been less concord at least for patients with HT – regarding other possible risk factors, including serum triglycerides, original ischemic cardiopathy, blood urea and alkaline phosphatase, weight, body mass index, race, donor hypertension, and pre-transplant hepatitis C infection (1, 9–12).

Here, we report risk factors for K/DOQI stage 3 CKD or worse that were identified by CAPRI, a cross-sectional observational study carried out in 14 Spanish heart transplant centers in late 2007 and early 2008 with the primary objective of determining the current prevalence of kidney dysfunction among Spanish patients with HT and risk factors therefore.

## Patients and methods

### Participants

Between October 2007 and March 2008, each of 14 Spanish heart transplant centers fed the CAPRI database with relevant data on all first patients with HT aged > 18 who presented during a pre-defined three-month period for a routine follow-up examination more than 30 d post-transplant (informed consent was a further condition that gave rise to no exclusions). Data were recorded for a total of 1062 patients (82.5% males) with a mean age of  $59.2 \pm 12.3$  yr and times since transplant ranging from one month to 22.3 yr (mean 6.7 yr, SD 4.6 yr). Before transplant, 15.0% had received a diagnosis of diabetes mellitus (cf. 26.5% at the time of the study), 29.8% were hypertensive (cf. 64.1% at study time), and 2.0% were seropositive for hepatitis C. The original cardiopathy leading to HT was dilated cardiomyopathy in 40.6%, and ischemic cardiomyopathy in 39.8%. Some 43.4% had suffered an episode of acute rejection of ISHLT grade 3A or worse in the first yr after transplant, and at the time of the study, 48.9% had been treated for cytomegalovirus infection. Table 1 lists details of immunosuppression at the time of the study.

**Table 1.** Immunosuppressive medication of 1062 Spanish patients with heart transplantation (HT)

Immunosuppressant	Prevalence (%)	
Calcineurin inhibitor		87.0
Cyclosporine	53.9	
Tacrolimus	33.1	
Antimetabolite		81.3
Azathioprine	11.7	
Mycophenolate	69.6	
Mycophenolate mofetil	66.7	
Sodium mycophenolate	2.9	
Steroids		68.3
mTOR inhibitor		20.2
Sirolimus	5.9	
Everolimus	14.3	

### Outcome variable

The outcome variable was K/DOQI stage 3 CKD or worse, hereinafter referred to for brevity as MSRD (moderate or severe renal dysfunction), and defined by the patients having an estimated glomerular filtration rate (eGFR) less than 60 mL/min per  $1.73 \text{ m}^2$ , or being on dialysis, or having undergone kidney transplant for post-HT kidney failure (4).

Glomerular filtration rate was estimated using the four-variable MDRD equation:  $\text{eGFR (mL/min per } 1.73 \text{ m}^2) = 186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times \text{Sex} \times \text{Race}$ ; where SCr is serum creatinine in mg/dL, Age is in yr, Sex is 0.742 if female and 1 if male, and Race is 1.21 if black and 1 otherwise (4).

### Statistical analysis

Patients with and without MSRD at the time of the study were compared with respect to relevant categorical variables by means of chi-squared tests, and with respect to continuous variables using Student's *t*-tests following verification of distributional normality by Kolmogorov–Smirnov tests. Independent predictors of MSRD at the time of the study were identified by means of backward stepwise multivariate logistic regression analysis of the data for the 977 patients for whom data were available for all the eight variables initially included in the model, to wit, all except two of the non-medication variables for which significant between-group differences had been detected in the univariate analyses (age at transplant; pre-transplant diabetes, hypertension, and serum creatinine; serum creatinine 30 d after transplant; and time since transplant – hypertension and diabetes at study time were omitted as redundant) plus sex and the occurrence of acute rejection of ISHLT grade  $\geq 3A$  in the first yr post-transplant (these last two being included on clinical grounds; see the Discussion). Variables were dropped from the model if  $p < 0.1$ . To investigate the possible influence of tacrolimus (Tac) as against cyclosporine (CsA), two

further multivariate logistic regressions were also performed on subsets of the 977, one including only the 924 patients started on CsA or Tac after transplantation, and the other only the 853 patients taking CsA or Tac at the time of the study. The variables included in these two regressions were seven that emerged as significant or near significant in the analysis of 977 patient (see Results; these seven were forced to remain in the model as possible confounders) plus either Tac versus CsA after transplantation, or Tac versus CsA at the time of the study. All statistical calculations were performed using SPSS for Windows v. 16.0. The criterion for statistical significance was  $p < 0.05$ .

## Results

The prevalence of MSRD in the study group at the time of the study was 61.4% (652/1062). Among the pre-transplant characteristics examined, the MSRD and non-MSRD groups differed significantly with respect to age at transplant (MSRD  $55.5 \pm 9.9$  yr, non-MSRD  $47.8 \pm 13.3$  yr;  $p < 0.001$ ), serum creatinine ( $1.35 \pm 0.63$  vs.  $1.13 \pm 0.47$  mg/dL;  $p < 0.001$ ), diabetes (17.9% vs. 10.2%;  $p = 0.001$ ), and arterial hypertension (34.5% vs. 22.2%;  $p < 0.001$ ), but not with respect to sex or the original cardiopathy that had led to HT (Table 2). Among other variables of potential utility for prediction of MSRD, the MSRD and non-MSRD groups differed significantly with respect to serum creatinine 30 d after transplant (MSRD  $1.35 \pm 0.73$ , non-MSRD  $1.06 \pm 0.38$ ;  $p < 0.001$ ) and the time elapsed between transplant and study ( $7.1 \pm 4.7$  vs.  $6.0 \pm 4.4$  yr;  $p < 0.001$ ), but not with respect to seropositivity for hepatitis C virus, or treatment for cytomegalovirus infection, or the incidence of acute rejection  $\geq$  ISHLT grade 3A in the first yr after transplant (Table 2).

**Table 2.** Comparisons with respect to non-medication variables between patients with heart transplantation (HT) with and without moderate or severe renal dysfunction (MSRD) at the time of the study

Variable	Non-MSRD	MSRD	p-value
Pre-transplant			
Male sex	84.4	81.3	0.214
Age at transplant (yr)	47.8 (13.3)	55.5 (9.9)	<0.001
Original cardiopathy			
Dilated cardiomyopathy	44.1	38.3	0.084
Ischemic cardiomyopathy	35.4	42.6	
Others	20.4	19.0	
Serum creatinine (mg/dL)	1.13 (0.47)	1.35 (0.63)	<0.001
Diabetes mellitus	10.2	17.9	0.001
Arterial hypertension	22.2	34.5	<0.001
Post-transplant			
Serum creatinine 30 d post-HT (mg/dL)	1.06 (0.38)	1.35 (0.73)	<0.001
Hepatitis C virus	1.2	2.5	0.181
Cytomegalovirus infection	45.7	50.9	0.101
Acute rejection $\geq$ grade 3A in the first yr	40.4	45.4	0.127
At the time of the study			
Arterial hypertension	54.6	70.0	<0.001
Diabetes	20.2	30.5	<0.001
Time since transplant (yr)	6.0 (4.4)	7.1 (4.7)	<0.001

Data are percentages, or means with standard deviations in parentheses.

In both groups, the prevalences of both arterial hypertension and diabetes at the time of the study were about double what they had been before transplant, increasing the difference between the two groups with respect to these variables.

There were also significant differences between the MSRD and non-MSRD groups as regards their immunosuppressive regimens, both at initiation of immunosuppression and at the time of the study; in particular, at both times, smaller proportions of the MSRD group received Tac (Table 3). Additionally, larger proportions of the MSRD group were started on CsA and azathioprine and a smaller proportion on mycophenolate; and at study time, the prevalence of immunosuppression with sirolimus or everolimus was greater in the MSRD group, and the prevalence of azathioprine was smaller (Table 3).

**Table 3.** Comparisons between patients with heart transplantation (HT) with and without MSRD at the time of the study with respect to immunosuppressive medication used for initiation of immunosuppression, and immunosuppressive medication at the time of the study

Variable	Non-MSRD	MSRD	p
At initiation			
Induction with antibodies	77.8	81.4	0.156
Steroids	95.9	97.2	0.222
Cyclosporine	75.6	80.8	0.045
Tacrolimus	19.5	13.5	0.01
Azathioprine	34.9	43.1	0.008
Mycophenolate	61.5	50.6	<0.001
Sirolimus	1.7	1.7	1
Everolimus	2.2	3.1	0.445
At study time			
Steroids	65.4	70.1	0.119
Cyclosporine	51.7	55.2	0.283
Tacrolimus	38.0	30.1	0.007
Azathioprine	14.9	9.7	0.011
Mycophenolate	72.9	67.5	0.065
Sirolimus	3.9	7.2	0.032
Everolimus	11.0	16.4	0.015

Data are given in percentages.

The significant independent predictors of MSRD identified in the initial multivariate logistic regression analysis of data for 977 patients (see Patients and methods) were female sex, age at transplant, time since transplant, and serum creatinine before and 30 d after transplant ( $p \leq 0.001$  in all cases; odds ratios (ORs), and their 95% confidence intervals (CIs) are listed in Table 4). Additionally, pre-transplant diabetes (OR 1.49, 95% CI 0.97–2.29;  $p = 0.066$ ) and acute rejection  $\geq$  grade 3A in the first yr (OR 1.31, 95% CI 0.98–1.77;  $p = 0.072$ ) came near to statistical significance. When all these variables were adjusted in the multivariate analysis that included the variable Tac vs. CsA at institution of immunosuppression, Tac vs. CsA was not significant (OR 0.755, 95% CI 0.501–1.140;  $p = 0.182$ ). However, in the analysis of data for 853 patients taking CsA or Tac at the time of the study, Tac vs. CsA emerged as a significant independent predictor alongside all the other variables except pre-transplant diabetes and acute rejection, Tac being less associated with MSRD than CsA (OR 0.65, 95% CI 0.46–0.90;  $p = 0.011$ ).

**Table 4.** Variables with significant or near-significant association with MSRD in a multivariate logistic regression in which the initial variables were those shown here plus pre-transplant hypertension

Variable	OR	95% CI	p value
Male sex	0.519	0.346 – 0.777	0.001
Pre-transplant serum creatinine (per mg/dL)	2.022	1.375 – 2.972	<0.001
Age at transplant (per yr)	1.060	1.046 – 1.074	<0.001
Serum creatinine 30 d post-HT (per mg/dL)	4.025	2.588 – 6.260	<0.001
Time since transplant (per yr)	1.077	1.043 – 1.113	<0.001
Pre-transplant diabetes	1.494	0.974 – 2.292	0.066
Acute rejection $\geq$ grade 3A in the first yr	1.314	0.976 – 1.768	0.072

OR, odds ratio, CI, confidence interval.

The analysis included data for the 977 patients for whom data were available for all eight variables.

Suspecting, in view of the general evolution of immunosuppressive regimens, that this last result might be because of early patients with HT having received larger dosages of cyclosporine than later patients, we repeated this analysis including only the 633 patients treated after the introduction of tacrolimus 9 yrs before the study date, but the only noteworthy change in the results was that time since transplant was no longer a significant predictor; in particular, the influence of Tac vs. CsA was almost unaltered (OR 0.68, 95% CI 0.47–0.98;  $p = 0.038$ ).

## Discussion

The risk factors for post-HT MSRDR identified in this work were female sex, age at transplant, time since transplant, serum creatinine before and 30 d after transplant, and current maintenance on CsA rather than Tac. These factors mostly coincide with those identified in other studies of renal dysfunction among patients with HT and other non-renal solid organ transplant patients.

The variables of the initial models employed in the regression analyses from which these predictors emerged included sex and acute rejection in the first yr, in spite of these variables not having differed significantly between the MSRDR and non-MSRDR groups in the corresponding univariate analyses. Sex was included fundamentally because female sex has frequently emerged as a significant risk factor in other studies; and acute rejection in the first yr because of its probably having given rise to the maintenance of larger doses of CNI, which in this study would make it a confounder.

Conversely, the multivariate analyses did not include immunosuppressive variables with respect to which the two groups *had* differed significantly in univariate analyses (with the exception of Tac vs. CsA in the last three multivariate analyses). Calcineurin inhibitors as a class were at first excluded because they are the root cause of post-transplant MSRDR and were in any case initially administered to 95% of patients; while between-group differences in other immunosuppressants were regarded either as a consequence of concomitant differences in time since transplant and/or calcineurin inhibitor dosage or as a result of changes in therapy because of the detection of renal dysfunction (and hence not as risk factors). Thus, although the proportion of patients started post-operatively on azathioprine was larger in the MSRDR than the non-MSRDR group and the proportion started on mycophenolate smaller, we assume that this was partly because of the MSRDR group having undergone transplantation at a slightly earlier date; and also, more decisively, to mycophenolate generally having been accompanied by lower doses of calcineurin inhibitors than azathioprine, as a consequence of which azathioprine-treated patients would be more likely to progress to MSRDR (13). At the time of the study, the proportion of patients on azathioprine was smaller in the MSRDR group, which we assume to have been because of the fact that for some yr, our centers, in view of our own experience (13) and the results of the IMPROVED study (14), have responded to renal dysfunction by switching patients from azathioprine to mycophenolate, with reduction or replacement of CNI. The greater prevalence of mTOR inhibitors in the MSRDR group at study time is likewise attributable to their having been prescribed in response to the detection of renal dysfunction (15). By contrast, the inclusion of the variable Tac vs. CsA in the three final multivariate analyses is justified because in none of the 14 participating centers has it been standard practice to replace CsA with Tac in response to renal dysfunction.

Age at transplant has emerged as a risk factor in numerous studies (1, 5, 11, 16–19), even though the definition of renal dysfunction has varied considerably, from serum creatinine  $> 1.5$  mg/dL (16) to GFR  $< 20$  mL/min per  $1.73$  m<sup>2</sup> (19). Age is in fact expected to predict almost any GFR-based concept of renal dysfunction, since GFR in the general population aged  $> 30$  falls by about 1 mL/min per  $1.73$  m<sup>2</sup> per yr (4). Interestingly, age was not an independent predictor in two studies in which the criterion variable was end-stage renal disease (ESRD) (20, 21).

As noted above, female sex is also a risk factor for renal dysfunction that has been observed in many studies (4, 12, 17, 18), and which patients with HT “inherit” from the general population, where GFR is said to be around 8% less in women than in men (4). In the only study we know in which male sex rather than female sex emerged as a risk factor (16), this finding may have been related to the criterion for renal dysfunction having been very lax (serum creatinine  $> 1.5$  mg/dL) and/or to all patients having had normal pre-transplant serum creatinine values.

Time since transplant is likewise expected to increase the risk of renal dysfunction, partly because it contributes to age, and partly because it implies longer exposure to CNI for patients taking these drugs.

Another known risk factor for CKD – and for post-operative death (22) – is post-operative acute kidney injury (AKI), especially if renal replacement therapy is required for its reversal (5, 18). Whereas recovery from properly treated AKI is generally virtually total among non-transplant patients, it is hindered in transplant patients by immunosuppressive medication and by any functional underperformance by the transplanted organ (23). Post-operative AKI was not considered as such in the present study, but will no doubt have contributed to the influence of serum creatinine concentration 30 d

post-HT, which must also reflect the reported influence of a sharp decline in renal function in the first three months after transplant (24). The emergence of pre-transplant serum creatinine as a risk factor independent of 30 d post-HT creatinine may also be due in part to the influence of the former on the incidence of post-operative AKI (22, 25).

Although the calcineurin inhibitors Tac and CsA were not found to differ in their renal effects in two short-term (12–18-month) multicenter studies in which 314 patients were randomized to one or the other (26, 27), there is increasing evidence that Tac not only improves blood lipid profile, but is also less renoaggressive than CsA following HT, at least as regards stabilization or improvement of GFR and serum creatinine (5, 12, 28–31). This conclusion appears to be supported by the results of the present study (in which the mean time since transplant was 6.7 yr): Tac was used by a greater proportion of non-MSRD than patients with MSRD both post-operatively and at the time of the study, and CsA by larger proportions of patients with MSRD than non-MSRD patients (Table 3); and Tac versus CsA at study time emerged as a significant predictor in the multivariate analyses in which it was included. Although it is not clear why Tac versus CsA at the institution of immunosuppression was not a significant predictor, this negative result may derive from Tac originally having been prescribed mainly to female patients – who are more prone to renal dysfunction – on account of the hirsutism associated with CsA (results not shown).

The above results must of course be considered with caution owing to the cross-sectional nature of this study. In particular, it is difficult to judge the extent to which they may have been affected by selective survival; for example, selective survival may have led to such acknowledged risk factors as diabetes, hypertension, and hyperlipidemia not emerging as such in this study. Also, although a distinction was made between post-operative immunosuppression and immunosuppression at the time of the study, no attempt was made to take into account the time point at which conversion from CsA to Tac may have taken place, changes in other reno-relevant medication (immunosuppressives, anti-hypertensives, etc.), or drug dosages or serum levels (though it is unlikely that generally recommended dosages can have been departed from). Nevertheless, none of the positive findings clashes with the recent literature in the field, and the lesser nephrotoxic risk of Tac at the time of the study emerged in spite of the above-noted greater prevalence of immunosuppression with Tac among female patients, who are more likely to progress to MSRD.

In conclusion, in this cross-sectional study of 1062 patients with HT, female sex, age, and serum creatinine at transplant, serum creatinine a month after transplant, time since transplant, and current use of CsA rather than Tac all emerged as statistically independent predictors of K/DOQI chronic kidney disease of stage 3 or worse. These findings should be tested further in prospective longitudinal trials.

### **Authorship**

Designed study: Juan F. Delgado and MG Crespo. Performed study and collected data: J. F. Delgado, M. G. Crespo-Leiro, Miguel A. Gómez-Sánchez, M. J. Paniagua, F. González, J. A. Vázquez, J. Fernández, D. Pascual, L. Almenar, L. Martínez, B. Díaz, E. Roig, J. Segovia, J. M. Arizón, I. Garrido, T. Blasco, J. López, V. Brossa and N. Manito. Analyzed data: Javier Muñoz. Wrote the paper: Juan F. Delgado.

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## Appendix

The following institutions and researchers participated in the CAPRI study (listed in descending order of the number of patients enrolled).

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